REMARKS

As recited in Claim 25, the present invention is an oral or dermal medicinal composition containing a pharmaceutical active substance and a thermoplastic coating and binding agent prepared by a method of applying a thermoplastic coating and binding agent in a hot-melt liquid state at a temperature of 100-150°C to said oral or dermal medicinal composition, followed by cooling to solidify the thermoplastic coating and binding agent, wherein said thermoplastic coating and binding agent consists essentially of a mixture of, based on 100% by weight of A and B:

A) a thermoplastic acrylic plastic with a melting temperature above room temperature and below 200°C, a glass transition temperature below 120°C, and a melt viscosity of 1,000 to 1,000,000 Pa-sec at the melting temperature; and

B) 20-50 wt.% of glycerol monostearate, wherein the glass transition temperature of the mixture is no more than 20°K below the glass transition temperature of component A.

The Declaration under 37 C.F.R. § 1.132 of named co-inventor Manfred Assmus, filed June 21, 1999 (first Assmus Declaration), and the Supplemental Declaration of Assmus, filed October 5, 1999 (supplemental first Assmus Declaration), demonstrate the significance of a number of the above-recited limitations.

The first Assmus Declaration demonstrates that the combination of a thermoplastic acrylic plastic within the terms of component A, combined with amounts of glycerol monostearate (GMS), now flow improver component B, in amounts from 20 to 80 wt% of GMS, based on the combination of components A and B, when heated to a temperature of 60°C, 65°C, or 80°C respectively, does not produce an (absolutely) clear and homogeneous melt, such as obtained with a temperature of at least 100°C, as required by the present claims. In addition, the first Assmus Declaration shows that the properties of the product produced, and thus the product itself, changes both by the relative amount of GMS present and the

temperature at which the thermoplastic coating and binding agent is applied. The supplemental first Assmus Declaration shows how the heating temperature for, *inter alia*, 50% GMS and 80% GMS, affects the structure of the polymer particles produced. The results show no interaction between the GMS flow improver and the polymer at 65°C; the beginning of interaction at 100°C; and strong interaction at 150°C.

The above-discussed data could not have been predicted by the applied prior art.

The rejection of Claims 25-28 under 35 U.S.C. § 102(b) as anticipated by the article *Drugs Made in Germany* (Petereit et al), is respectfully traversed. Petereit et al discloses fast disintegrating controlled release tablets from coated particles, wherein the coating is provided with aqueous dispersions of methacrylic acid and methacrylic ester copolymers, including various Eudragit brand products. Petereit et al further discloses the admixture of 25-50% of tableting excipients and other components. Under the second "IT", GMS is listed among a relatively large number of materials, including various Eudragit brand materials.

The Examiner has interpreted the above-discussed disclosure in Petereit et al as inclusive of pharmaceutical particles coated with a Eudragit brand copolymer and from 25-50% of GMS. Applicants respectfully disagree with the Examiner's interpretation. The Examiner assumes that all of the materials listed under the second IT each represent a singular component present in an amount of 25-50% of a coating composition. This is clearly incorrect, since various Eudragit brand products are listed therein as well. Rather, the materials listed under the second IT appear to be materials described in the complete article of which Petereit et al is only an abstract. Petereit et al neither discloses nor suggests a coating containing 25-50% by weight of GMS.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,707,646 (Yajima et al), is respectfully traversed. Yajima et al discloses a taste masking

pharmaceutical composition obtained by melting a substance having a low melting point under heat at a temperature equal to or higher than the melting point thereof, dispersing or dissolving a functional polymer compound in the resultant molten substance to form a composition, melt- or heat-granulating the composition and an unpleasantly tasting basic drug to form a complex and incorporating sugar alcohol and basic oxide to the complex (column 2, lines 25-37). Yajima et al lists various Eudragit brand polymers as the functional polymer (column 2, lines 59-61), and GMS as among preferred substances having a low melting point (column 3, lines 5-6). Yajima et al further discloses that the amount of the functional polymer in the complex is 1-60% by weight, and that the amount of the complex in the composition is 20-60% by weight. While Yajima et al discloses further the percentages of other ingredients, no percentage range is described for the low melting point substance. The Examiner particularly relies on Examples 4, 7 and 13, all of which describe the combination of Eudragit E and GMS. However, in Examples 4, 7 and 13, the percentage of GMS, based on the total amount of GMS and Eudragit E, is 600/700 × 100, or about 86%. Without the present disclosure as a guide, there would have been no motivation to adjust the relative amounts of GMS and Eudragit E in Yajima et al so that the amount of GMS is present as 20-50% by weight of the combination. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration. While the Examiner holds that it would have been obvious to employ the GMS of Yajima et al within the presently-recited range "for low levels of the drug," no nexus is evident in Yajima

et al regarding relative amounts of low melting point substance and functional polymer compound vis-à-vis the amount of drug.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,188,838 (Deleuil et al), is respectfully traversed. Deleuil et al is drawn to a process for converting into pearl form a pharmaceutical active substance exhibiting an indefinite crystallization point, which is mixed with one or more pharmaceutical excipients in molten form, the melt is forced to pass through a nozzle which is subject to vibration, the pearls formed are allowed to fall in a tower counter current-wise to a gas, and the solid pearls are collected in the bottom of the tower (column 2, lines 12-20). Such active substances thus exhibit a supercooling phenomenon. Deleuil et al discloses a long list of additives which enable the crystallization of the supercooled product to be induced, such as "glycerol stearate" marketed under the mark Precirol (column 2, lines 43-44), and as shown in Table 1 in Tests 1-5, in an amount from 25-50%. (Pöllinger et al, *infra*, discloses that Precirol is a mixture of mono-, di- and triesters of palmitic acid and stearic acid with glycerol, at column 6, lines 20-21.) Deleuil et al discloses further that it is sometimes desirable to add polymers which are soluble or dispersible in the melt, which will permit a completely controlled and adjustable dissolution of the pearls when they are used, among which polymers are included acrylic resins such as Eudragit brand resins (column 3, lines 15-23). None of the examples in Deleuil et al employ any acrylic resin. However, Test 10 uses ethyl cellulose in an amount of 3.5%, which ethyl cellulose is disclosed as an applicable polymer (column 3, lines 20-22). Thus, to the extent Deleuil et al discloses the combination of an additive and a polymer, the additive, e.g., Precirol, which according to Pöllinger et al contains GMS in some undefined amount, would be present in significantly greater amounts than the additive, e.g., Eudragit brand polymer. Without the present disclosure as a guide, one skilled in the art would not

have selected the presently-recited components A and B in the relative amounts required by the present claims. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,603,957 (Burguiere et al) in view of U.S. 5,552,159 (Mueller et al) is respectfully traversed. Burguiere et al discloses controlled-release microcapsules of acetylsalicylic acid, containing a coating which is obtained from a coating composition comprising at least one film-forming polymer insoluble in the gastrointestinal environment (column 5, lines 44-45), such as a Eudragit brand polymer (column 6, lines 7-13), in an amount of 60-85% by weight (column 5, line 56); at least one water-soluble polymer; at least one solid lubricating filler; and at least one hydrophobic plasticizer, which may be a stearate of a glycol such as glycerol (column 6, lines 33-36), which plasticizer is present in an amount of 2-20, preferably 5-15, wt% (column 5, line 60). Burguiere et al further discloses that their microcapsules are obtained by a process consisting essentially of preparing the coating composition components by mixing them in a solvent system, applying the mixture to particles of acetylsalicylic acid, drying the resulting microcapsules, and if appropriate, mixing the latter with at least one anti-caking agent (column 7, lines 14-21). Mueller et al discloses a solid depot drug form comprising a pharmaceutical active ingredient and a polymer melt comprising at least one water-insoluble poly(meth)acrylate with a glass transition temperature in the range from -60° to 180°C such as

a Eudragit brand polymer, and either a particular water-soluble hydroxyalkyl cellulose or hydroxyalkylmethyl cellulose or an N-vinylpyrrolidone polymer.

While Mueller et al discloses a solid depot drug form produced by melt extrusion at from 50° to 200°C, Mueller et al discloses and suggests nothing with regard to the presently-recited requirement of a hot-melt liquid state at a temperature of 100-150°C, nor the presently-recited GMS, nor the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*.

Without the present disclosure as a guide, one skilled in the art would not have combined Burguiere et al and Mueller et al. Nor could one skilled in the art have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over U.S. 5,858,412 (Staniforth et al) in view of Mueller et al, is respectfully traversed. Staniforth et al discloses a sustained-release formulation comprising an active ingredient, an augmented microcrystalline cellulose which possesses excellent compressibility, and a sustained-release carrier (column 5, lines 4-15). Staniforth et al discloses further that one or more compressibility augmenting agents may be present (column 6, lines 26-31). Staniforth et al discloses a wide variety of compressibility augmenting agents, beginning at column 7, line 64, among which are a relatively long list of surfactants, including GMS (column 11, line 33). Staniforth et al further discloses Eudragit brand polymers as applicable sustained release carriers (column 20, lines 29-31). The relatively large numbers of applicable combinations of ingredients in Staniforth et al is so large that it would not have even been *prima facie* obvious

to choose the combination of a Eudragit brand polymer and GMS, forgetting about all the other limitations of the present claims. See *In re Baird*, 29 USPQ 2d, 1550 (Fed. Cir. 1994) **(copy enclosed)**.

Mueller and its deficiencies have been discussed above.

Without the present disclosure as a guide, one skilled in the art would not have combined Staniforth et al and Mueller et al. Moreover, even if combined, the result would not have been the presently-claimed invention. See *Baird, supra*. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over JP 51-91317 (JP '317), U.S. 5,484,608 (Rudnic et al), and U.S. 5,695,784 (Pöllinger et al) in view of Petereit et al, Burguiere et al and Mueller et al, is respectfully traversed. JP '317 discloses pharmaceutical tablets or granules coated with a composition comprising a particularly specified polymer, a water-insoluble non-ionic surfactant solid at ambient temperature, and a higher fatty acid solid at ambient temperature. GMS is disclosed as a preferred non-ionic surfactant. No amounts of non-ionic surfactant are disclosed. Rudnic et al discloses a sustained-release pharmaceutical composition comprising a highly soluble pharmaceutical agent in a pharmaceutical carrier comprising a hydrophilic polymer, such as a Eudragit brand polymer (column 2, lines 50-61) in a hydrophobic matrix, including GMS (column 2, line 62 ff). While the Examiner relies on Example 1 therein, which contains a matrix component in

an amount of 20%, other examples, i.e., Examples 2 and 3, which specifically discloses GMS, contain GMS in an amount of 5%. There is no disclosure or suggestion to use GMS in an amount as high as 20% in Rudnic et al. Pöllinger et al discloses a flavor-masked pharmaceutical composition in the form of microcapsules prepared using specific coatings (column 3, lines 23-27). While Pöllinger et al lists various film-forming agents known in the art (column 4, line 45 ff), only some Eudragit brand, but not all Eudragit brand, polymers may be used in Pöllinger et al (column 4, line 66 ff). For example, Eudragit brand polymers that are cationic did not produce the desired results (column 5, line 44 ff). Pöllinger et al discloses further that plasticides may be included, among which are GMS (column 5, lines 49-57, especially line 53). None of the examples in Pöllinger et al contain GMS and thus, no percentage range therefore is disclosed.

The disclosures and deficiencies of Petereit et al, Burguiere et al, and Mueller et al have been discussed above.

One skilled in the art would not have combined the above-applied prior art without the present disclosure as a guide. Moreover, even if combined, the result would still not be the presently-claimed invention. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

The rejection of Claims 25-28 under 35 U.S.C. § 103(a) as unpatentable over Mueller et al in view of Petereit et al and Burguiere et al, is respectfully traversed. The disclosures and deficiencies of each of these references have been discussed above. First of all, Petereit

et al do not disclose the function of the GMS therein. Burguiere et al discloses a maximum of 20% by weight of plasticizer, and preferably a maximum of 15%. A plasticizer is not even required in Mueller et al. Without the present disclosure as a guide, one skilled in the art would not have combined the above-applied references. Moreover, even if combined, the result would still not be the presently-claimed invention. Nor could one skilled in the art have arrived at the presently-recited requirement that the glass transition temperature of the mixture of thermoplastic acrylic plastic and GMS be no more than 20°K below the glass transition temperature of the thermoplastic acrylic plastic *per se*, or have predicted the importance of both the hot-melt temperature and relative amounts of GMS present, as demonstrated in the above-discussed first Assmus Declaration and supplemental first Assmus Declaration.

For all the above reasons, it is respectfully requested that this rejection be withdrawn.

Applicants respectfully submit that all of the presently pending and active claims in this application are now in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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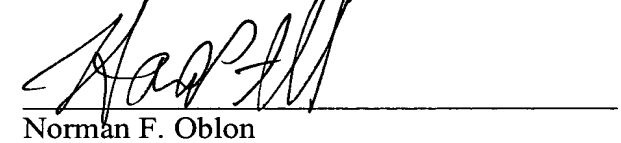

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